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Effects and cost of different strategies to eliminate hepatitis C virus transmission in Pakistan: a modelling analysis



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Summary

Background The WHO elimination strategy for hepatitis C virus advocates scaling up screening and treatment to reduce global hepatitis C incidence by 80% by 2030, but little is known about how this reduction could be achieved and the costs of doing so. We aimed to evaluate the effects and cost of different strategies to scale up screening and treatment of hepatitis C in Pakistan and determine what is required to meet WHO elimination targets for incidence.

Methods We adapted a previous model of hepatitis C virus transmission, treatment, and disease progression for Pakistan, calibrating using available data to incorporate a detailed cascade of care for hepatitis C with cost data on diagnostics and hepatitis C treatment. We modelled the effect on various outcomes and costs of alternative scenarios for scaling up screening and hepatitis C treatment in 2018–30. We calibrated the model to country-level demographic data for 1960–2015 (including population growth) and to hepatitis C seroprevalence data from a national survey in 2007–08, surveys among people who inject drugs (PWID), and hepatitis C seroprevalence trends among blood donors. The cascade of care in our model begins with diagnosis of hepatitis C infection through antibody screening and RNA confirmation. Diagnosed individuals are then referred to care and started on treatment, which can result in a sustained virological response (effective cure). We report the median and 95% uncertainty interval (UI) from 1151 modelled runs.

Findings One-time screening of 90% of the 2018 population by 2030, with 80% referral to treatment, was projected to lead to 13·8 million (95% UI 13·4–14·1) individuals being screened and 350 000 (315 000–385 000) treatments started annually, decreasing hepatitis C incidence by 26·5% (22·5–30·7) over 2018–30. Prioritised screening of high prevalence groups (PWID and adults aged ≥30 years) and rescreening (annually for PWID, otherwise every 10 years) are likely to increase the number screened and treated by 46·8% and decrease incidence by 50·8% (95% UI 46·1–55·0). Decreasing hepatitis C incidence by 80% is estimated to require a doubling of the primary screening rate, increasing referral to 90%, rescreening the general population every 5 years, and re-engaging those lost to follow-up every 5 years. This approach could cost US\$8·1 billion, reducing to \$3·9 billion with lowest costs for diagnostic tests and drugs, including health-care savings, and implementing a simplified treatment algorithm.

Interpretation Pakistan will need to invest about 9·0% of its yearly health expenditure to enable sufficient scale up in screening and treatment to achieve the WHO hepatitis C elimination target of an 80% reduction in incidence by 2030.

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Introduction

After the development of highly effective direct-acting antiviral treatments for hepatitis C, WHO developed a Global Health Sector Strategy to eliminate hepatitis C as a public health threat, setting targets to reduce the incidence of new hepatitis C infections by 80% and hepatitis C-related mortality by 65% by 2030 (compared with 2015 levels).¹ In low-income and middle-income countries (LMICs), which account for 50–80% of the global hepatitis C burden,^{2,3} diagnosis rates are low (13·9%), with 7·1% of people (569 million) starting treatment in 2015, most of which occurred in Egypt.³

Pakistan has the second largest hepatitis C burden worldwide, with an estimated 7·0 million infections

in 2013.^{4,5} Treatment is often insufficient, leading to increasing hepatitis C-related morbidity.^{5,6} Pakistan's hepatitis C epidemic is generalised, with most hepatitis C transmission being attributable to routine community and medical-related practices.^{7,8}

Since 2005, national and provincial hepatitis control programmes have been treating hepatitis C-infected patients, with about 150 000–160 000 patients starting treatment annually by 2015.⁹ From 2016, direct-acting antiviral therapies became available in Pakistan, and both the public and private sectors have been starting programmes to scale up hepatitis C treatment.⁹ This scale up depends on identifying infected cases; however, it is unknown what levels of screening, linkage to care,

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Research in context

Evidence before this study

We searched PubMed for articles published between database inception and Aug 31, 2019, using the search terms ("HCV" OR "hepatitis C virus" OR "hep C") AND ("mathematical" OR "dynamic" OR "transmission") AND ("model" OR "models" OR "modelling" OR "modeling") AND ("case-finding" OR "screening" OR "treatment") AND ("cost" OR "costs" OR "costing"). No language restrictions were used. Many hepatitis C modelling studies have focused on projecting the effect and economic implications of testing and treatment interventions in specific subgroups, including people who inject drugs (PWID), men who have sex with men, and prisoners. A previous dynamic modelling approach studied the impact and cost-effectiveness of intervention packages to reduce HIV and hepatitis C infections among PWID in eastern Europe and central Asia, but did not consider levels of interventions that would reach elimination. Other studies have been done in high-income countries or have used static models (eg, Markov models) and so could not consider levels of treatment needed to reduce incidence. Only three studies presented cost-effectiveness or budget analyses of hepatitis C screening and treatment interventions in the general population of low-income and middle-income countries (LMICs), namely, Egypt, South Africa, and Pakistan. However, none of these studies used a dynamic modelling approach, nor did they consider the budgetary requirements for reducing country-level hepatitis C incidence to WHO-advocated elimination targets. The Pakistan analysis did not use locally collected cost data, which resulted in optimistic cost projections that are less representative of the Pakistan context.

Added value of this study

To our knowledge, this study is the first country-level estimation of the hepatitis C screening and treatment requirements, and associated costs, for achieving the WHO hepatitis C elimination

incidence targets in a generalised epidemic LMIC setting, specifically Pakistan. The accuracy of our projections is maximised through calibrating a detailed model to context-specific data from Pakistan, and in using real-world costs of screening and treatment for Pakistan. Our results provide valuable and practical new information on how each stage of the cascade of care for hepatitis C needs to be improved to achieve the WHO hepatitis C elimination target for incidence in Pakistan, and the costs of doing so. The implementation of effective hepatitis C screening strategies is also important, with our findings suggesting that prioritised screening of population subgroups with high prevalence of hepatitis C, such as adults and PWID, can improve the efficiency and effect of screening. These considerations will probably have a substantial effect on optimising the costs of achieving the WHO hepatitis C elimination targets, which our projections suggest will still be high with the cheapest available drug regimens and diagnostics. Importantly, our projections also show that substantial savings can be achieved through simplifying the screening and treatment pathway, a consideration that is relevant not only to Pakistan, but also to other LMICs.

Implications of all the available evidence

This study directly addresses the feasibility of eliminating hepatitis C at a country level, a prerequisite to achieving global elimination as set out by WHO. To achieve this aim, high screening coverage of the whole population is crucial, while strengthening all elements of the care continuum to ensure a high proportion of individuals are effectively cured. To minimise costs, screening strategies should prioritise testing and retesting in those with transmission potential and focus on maintaining high referral rates to ensure that diagnosed individuals are adequately linked to care and started on treatment.

and resources are needed to scale up treatment sufficiently to reach the WHO hepatitis C elimination targets by 2030.

We aimed to model the effects and cost of different strategies to scale up screening and treatment of hepatitis C in Pakistan, to determine what is required to reach the WHO hepatitis C elimination targets for incidence.

Methods

Model overview

We adapted a previous model of hepatitis C transmission, treatment, and disease progression for Pakistan⁵ to incorporate a detailed cascade of care for hepatitis C (figure 1, appendix pp 3–4). Consistent with the previous model, our new model incorporates population growth, age structure, and sex; hepatitis C transmission in the general population and among

people who inject drugs (PWID); and hepatitis C-associated disease progression.

Briefly, we divided the population into three age categories: young (0–19 years), young adult (20–29 years), and adult (≥ 30 years). Individuals enter the young category at a birth rate dependent on population growth and are initially deemed to be susceptible to hepatitis C. They transition through the age categories, with some young adults becoming PWID. Mortality is age-specific and sex-specific, with PWID experiencing heightened drug-related mortality.¹⁰ Susceptible individuals become hepatitis C-infected at a rate dependent on their sex, age, and hepatitis C prevalence in the population. PWID have additional infection risk. Most newly infected individuals become chronically infected and progress to compensated cirrhosis if left untreated, and eventually end-stage liver disease (ie, decompensated cirrhosis, and hepatocellular carcinoma). End-stage liver disease is associated with

See Online for appendix

increased mortality.¹¹ Reinfection can occur after successful treatment or spontaneous clearance.^{12,13}

The cascade of care in our model begins with diagnosis of hepatitis C infection through antibody screening and RNA confirmation. Diagnosed individuals are then referred to care and initiated on treatment, which can result in a sustained virological response (effective cure). We assume that, each year, a proportion of the population is screened for hepatitis C antibodies for the first time, with previously tested seronegative individuals having specified retesting rates that vary across subgroups. Individuals testing antibody-positive can receive RNA testing, whereupon they become diagnosed with active infection if they are RNA-positive. Any antibody-positive individuals who are not aware of their current infection status can also be rescreened via RNA testing. Depending on possible eligibility criteria or the prioritisation of certain subgroups, a proportion of newly diagnosed individuals are referred to treatment. If treated, patients either achieve sustained virological response or fail treatment, after which they can be retreated. Although loss to follow-up can occur along the cascade of care, re-engagement can result in such individuals re-entering the diagnosed category.

Baseline model parameterisation and calibration

The model was parameterised using demographic, behavioural, and hepatitis C epidemiological data from Pakistan (table 1, appendix pp 30–33). We calibrated the model to country-level demographic data for 1960–2015 (including population growth^{14,15}) and to hepatitis C seroprevalence data (by age group and overall) from a national survey⁷ in 2007–08 (4.8% overall), surveys among PWID^{16,17} (56–69%), and hepatitis C seroprevalence trends among blood donors. These previous data suggest hepatitis C seroprevalence increased by 0.39% (95% CI –0.17 to 0.94%) per decade for 1994–2014 (appendix p 14).

Data on hepatitis C disease progression and mortality came from the literature.⁴ Treatment before 2016 using interferon-based therapy (50–81% sustained virological response)¹⁸ was modelled using in-country data (table 1; appendix p 33); whereas direct-acting antiviral treatments (80–95% sustained virological response) were used post-2016.^{13,19} No data on screening exists for Pakistan, so we calibrated the mean screening rate (3.7% [95% UI 2.6–5.9]) to give the observed 150 000–160 000 treatments undertaken each year,⁹ while assuming a treatment referral rate of 35–70% based on Pakistan data.²⁰

Uncertainty distributions were associated with most parameters and calibration data (appendix pp 30–33); the only exceptions being some unknown parameters estimated during the model calibration. To calibrate the model, we randomly sampled these uncertainty distributions to produce 4000 paired sets of parameters and calibration data. For each set, the unknown model parameters were varied to fit the model to the sampled calibration data for chronic hepatitis C prevalence by age and for PWID using a non-linear least squares

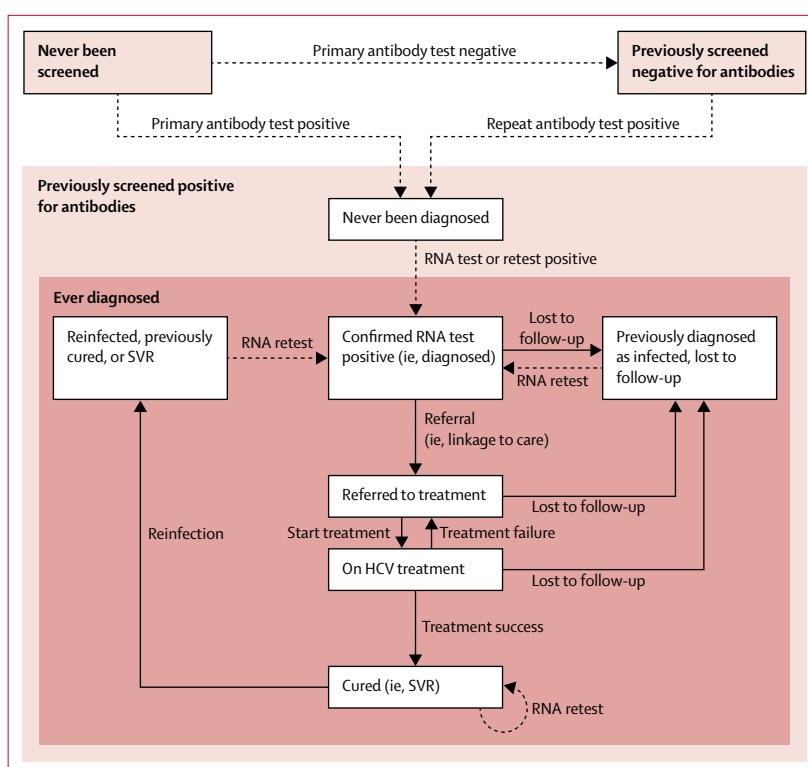


Figure 1: Simplified schematic of our HCV screening and treatment model

Solid lines indicate epidemiological transitions. Dashed lines indicate antibody or RNA (re)screening. Broadly, the population is split into three categories: those who have never been screened (and eligible for primary antibody screening); those who have been previously screened as antibody-negative (and are eligible for rescreening); and those who have been previously screened as antibody-positive. Individuals with known antibody-positive status are divided into two subcategories to indicate whether they have ever been diagnosed or not. The full HCV screening model schematic, including demographic and behavioural compartments, disease progression stages, HCV transmission dynamics, and the screening and treatment intervention cascade of care can be found in the appendix (pp 3–4). HCV=hepatitis C virus. SVR=sustained virological response.

optimisation algorithm in MATLAB (version 2018b; MathWorks, Natick, MA, USA). Parameter sets that did not produce model estimates within the 95% CI of the overall chronic hepatitis C prevalence from the 2007–08 national survey were discarded, which produced 1151 model fits that were used for subsequent analyses. We report the results as the median and 95% uncertainty interval (UI) from these modelled runs. Further details are given in the appendix (pp 13–18).

Model analyses

We used the calibrated model to evaluate various screening and treatment intervention scenarios from 2018. We assessed how each scenario improved the cascade of care for hepatitis C, and the percentage reduction in hepatitis C incidence and mortality by 2030 compared with 2015. Scenarios were also compared with a counterfactual of no treatment from 2018 (S0) and a status-quo scenario of maintaining current levels of treatment (150 000–160 000 treatments per year) until 2030 (SQ).

In each scenario, we assume that all individuals with an antibody-positive test are tested for hepatitis C RNA.

	Baseline value or fitted range	Source
Demographic parameters		
Mean population growth rate per year, median (95% UI)		
Before 2000	2.76% (2.53–2.99)*	Pakistan Economic Survey; ¹⁴ UN Department of Economic and Social Affairs, Population Division ¹⁵
2000–15	1.92% (1.54–2.31)*	Pakistan Economic Survey; ¹⁴ UN Department of Economic and Social Affairs, Population Division ¹⁵
After 2015	1.72% (uniform 1.35–2.08)	Pakistan Economic Survey; ¹⁴ UN Department of Economic and Social Affairs, Population Division ¹⁵
Proportion of young adults who start injecting drug use, median (95% UI)		
Men	0.032 (0.026–0.039)*	Calibrated to fit proportion of men aged 15–64 years who inject drugs: 0.7% ¹⁷
Women	0.009 (0.0004–0.017)*	Calibrated to fit proportion of women aged 15–64 years who inject drugs: 0.01% ¹⁷
Mean mortality		
Young	1/56	Based on a life expectancy at birth of 66 years in 2015, and adjusted in model calibration to give proportion in 2015: 44% ¹⁵
Young adult	1/41	Based on a life expectancy at birth of 66 years in 2015, and adjusted in model calibration to give proportion in 2015: 19% ¹⁵
Adult	Men 0.023 (0.020–0.026); women: 0.020 (0.017–0.024)*	Based on a life expectancy at birth of 66 years in 2015, and adjusted in model calibration to give proportion in 2015: 37% ¹⁵
Additional drug-related mortality, median (95% UI)	0.028 (log-normal 0.020–0.039)	Based on estimates of drug-related mortality across Asia ¹⁰
Transmission parameters		
HCV transmission rate per susceptible person in each age group, median (95% UI)		
Young (β_1)	0.059 (0.052–0.066)*	Fit to chronic prevalence in young people (aged 0–19 years) from 2007–08 Pakistan national survey ⁷ on viral hepatitis: 1.5%
Young adult (β_2)	0.053 (0.023–0.085)*	Fit to chronic prevalence in young adults (aged 20–29 years) from 2007–08 Pakistan national survey ⁷ on viral hepatitis: 3.2%
Adult (β_3)	0.12 (0.10–0.14)*	Fit to chronic prevalence in adults (aged ≥ 30 years) from 2007–08 Pakistan national survey ⁷ on viral hepatitis: 6.9%
Additional HCV transmission rate for injecting drug use, median (95% UI)	0.61 (0.51–0.74)*	Fit to chronic prevalence in PWID ¹⁶ in 2012: 62.2% (55.5–68.8)
Proportion of infections that spontaneously clear	0.26 (uniform 0.22–0.29)	Systematic review of spontaneous HCV clearance ¹²
Treatment parameters		
Treatment rate per capita before 2018†		
2005–10	57 500	Pakistan Health Research Council (Mahmood H, PHRC, personal communication)
2011	137 970	Pakistan Health Research Council (Mahmood H, PHRC, personal communication)
2012	129 398	Pakistan Health Research Council (Mahmood H, PHRC, personal communication)
2013	137 910	Pakistan Health Research Council (Mahmood H, PHRC, personal communication)
2014	115 920	Pakistan Health Research Council (Mahmood H, PHRC, personal communication)
2015–17	152 710	Pakistan Health Research Council (Mahmood H, PHRC, personal communication)
Mean duration on treatment		
Before 2016	24 weeks	WHO HCV Treatment Guidelines ¹³
2016 onward	12 weeks for pre-cirrhotic patients, 24 weeks for post-cirrhotic patients	WHO HCV Treatment Guidelines ¹³
SVR rate with interferon and ribavirin treatment	0.66 (uniform 0.50–0.81)	Studies on SVR rates for conventional HCV treatment in Pakistan ¹⁸
SVR rate with new direct-acting antiviral treatments	0.9 (uniform 0.80–0.95)	WHO HCV Treatment Guidelines; ¹³ review of direct-acting antivirals in Pakistan ¹⁹
Data are baseline values (range) unless otherwise stated. Rates are per year. HCV=hepatitis C virus. PHRC=Pakistan Health Research Council. PWID=people who inject drugs. SVR=sustained virological response. UI=uncertainty interval. *Fitted data shown as median (95% UI). †Calibrated to historical treatment rates, total estimated historical HCV treatments before 2018 are given, assuming a public and private sector split of 40:60% (appendix p 33). Direct-acting antivirals were available from 2016 onwards.		
Table 1: Main baseline model parameters with associated uncertainty ranges		

We then assume different proportions of referral of diagnosed individuals to treatment (ie, the referral rate), with the remainder being lost to follow-up. All referred patients start treatment, with those who do not achieve a sustained virological response being retreated. For simplicity, we only incorporate one event of loss to follow-up between diagnosis and referral, and believe that this assumption captures the effect of other forms of loss to follow-up between diagnosis and treatment.

Unpublished data from Pakistan suggest that there is relatively little loss to follow-up after treatment initiation (data not shown), which can be accounted for in our sustained virological response data in the intention-to-treat population. We assumed a treatment duration of 12 weeks unless post-cirrhotic (24 weeks). The intervention scenarios are described in the panel, with model parameters shown in table 2 and the appendix (pp 17–19).

Panel: Model scenarios**Scenario S0**

No further treatment from 2018 onwards.

Scenario SQ

While assuming a range of referral rates (35–70%), the mean screening rate (3.7% [95% UI 2.6–5.9] of population per year) is calibrated to maintain current levels of treatment (ie, status quo).

Scenario S1

One-time random screening of 90% of the 2018 Pakistan population by end of 2030, equating to about 6.2% screened annually, with 80% of diagnosed individuals referred to treatment. This is the screening target set by WHO.^{1,3}

Scenario S2

One-time screening (as in scenario S1), but prioritised first to individuals aged ≥30 years and people who inject drugs (PWID), who have increased hepatitis C prevalence, and then to the rest of the general population.

Scenario S3

Prioritised one-time screening (as in scenario S2), but with periodic RNA rescreening of cured individuals and those previously screened RNA-negative, and antibody rescreening of individuals previously screened antibody-negative. Rescreening starts from 2020 and occurs every 10 years for non-PWID and annually for PWID.

Scenario S4

Following these scenarios, we then determined what further improvements to the cascade of care are needed to reduce hepatitis C incidence by 80% by 2030. These improvements include prioritised one-time screening as in scenario S3, but with increased referral to care (90%), double the primary antibody screening rate (12.4% per year), rescreening every 5 years for non-PWID, and re-engaging those who were lost to follow-up (every 5 years for non-PWID and yearly for PWID; not included previously).

	Antibody screening and rescreening			RNA rescreening of antibody-positive individuals				Referral: proportion of those diagnosed with hepatitis C who were linked to treatment (all)
	Primary antibody screening* (all)	Rescreening of SVR and previously screened uninfected*		Previously treated		Proportion of those diagnosed with hepatitis C who were lost to follow-up then linked back to care		
		General population	PWID	General population	PWID	General population	PWID	
Scenario S0
Scenario SQ	2.6–5.9%	35–70%
Scenario S1	6.2% (6.1–6.3)	80%
Scenario S2	6.2% (6.1–6.3)	80%
Scenario S3	6.2% (6.1–6.3)	10%	100%	10%	100%	80%
Scenario S4	12.4% (12.1–12.6)	20%	100%	20%	100%	20%	100%	90%

An annual primary screening rate of 6.2% (6.1–6.3) is equivalent to first-time antibody screening of 180 million (175–185) individuals, or 90% of the 2018 population, by 2030. Doubling this annual primary screening rate to 12.4% (12.1–12.6) is equivalent to first-time antibody screening of 280 million (265–290) individuals, or 140% of the 2018 population, by 2030. General population refers to individuals who do not inject drugs. PWID=people who inject drugs. SVR=sustained virological response. *We assume that all people who tested antibody-positive, either from primary antibody screening (ψ_1) or antibody rescreening (ψ_2), are subsequently tested for hepatitis C virus RNA (ie, there is no loss to follow-up at this stage).

Table 2: Model parameters for each screening and treatment intervention scenario, 2018 onwards

Estimation of screening and treatment costs

We estimated the total costs of each scenario to assess the affordability of widespread hepatitis C screening and treatment scale up. Cost data for undertaking hepatitis C testing and treatment (including materials, equipment, and staff time) came from a Médecins Sans Frontières hepatitis C treatment clinic in Machar Colony, Karachi from 2016 to 2017.^{21,22} A patient-level costing analysis was done using a provider's perspective in 2018 US\$ (appendix pp 16–17, 34–39). Treatment costs were adapted for generic sofosbuvir (\$15 for 28-day supply³) and daclatasvir (\$21 for 28-day supply),

giving a total treatment unit cost of \$403 for a 12-week treatment course and \$586 for 24 weeks, inclusive of drug, visit, and laboratory costs. All costs were valued at local rates. Screening unit costs were estimated to be \$10–17 per antibody test and \$34–41 per RNA test, including staff costs. Actual test kits were \$2.15 for antibody testing and \$24.09 for RNA testing. Healthcare costs for management of hepatitis C disease (other than curative treatment) were not included in the baseline cost estimates owing to a lack of data for Pakistan, but have been considered in the sensitivity analyses using adjusted costs from Cambodia (appendix

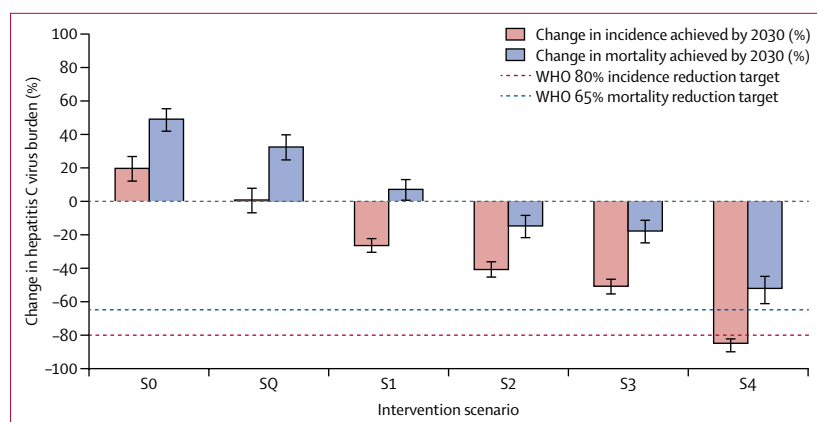


Figure 2: Relative change in incidence and mortality achieved by 2030 versus 2015, by intervention scenario Data are the median of 1151 final model runs. Error bars are 95% uncertainty intervals. Scenario S0: no screening or treatment from 2018 onwards. Scenario SQ: maintaining status quo treatment of 150 000–160 000 annual treatments from 2018. Scenario S1: one-time random screening of 90% of the general population of Pakistan by 2030, with 80% referral to care. Scenario S2: scenario S1 plus prioritised screening of people aged ≥ 30 years and PWID. Scenario S3: scenario S2 plus rescreening of cured and previously antibody-negative or RNA-negative individuals from 2020 (every 10 years for non-PWID and annually for PWID). Scenario S4: scenario S3 with incremental improvements to achieve elimination. PWID=people who inject drugs.

p 35). We also estimated the cost per cure for each strategy. Costs and outcomes were discounted at 3.5% per year. More details are given in the appendix (pp 16–17, 34–39).

Sensitivity analyses

We did sensitivity analyses to determine how the total costs of scenario S4 would vary for the following changes in cost assumptions: X1: assume lowest Pakistan direct-acting antiviral drug costs (\$18 vs \$109 for 12 weeks); X2: assume lowest costs for diagnostic test kits (\$0.40 vs \$2.15 for antibody test, \$15 vs \$24 for RNA confirmation); X3: include savings in health-care costs for managing patients with hepatitis C-related disease—cost data from Cambodia adjusted to the Pakistan context (pre-cirrhosis: \$15, compensated cirrhosis: \$47, decompensated cirrhosis: \$278, hepatocellular carcinoma: \$339, compared to no health-care costs in the base case); X4: include costs for improving referral from 80% to 90% of diagnosed chronic infections and re-engaging people who have been lost to follow-up (\$19 per patient referred or re-engaged, derived from assuming half a day of nurse time required to follow-up each patient); X5: include savings from implementing a simplified treatment pathway (reduced visits and laboratory investigations); X6: combine X1 to X5; and X7 and X8: no discount rate or double the discount rate for costs and outcomes (3.5% in base analyses). Further details are given in the appendix (p 35).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Without treatment from 2018 (S0), our model projects that prevalence of chronic hepatitis C will rise from 3.7% (95% UI 3.4–4.0) in 2018 to 4.5% (4.0–5.1) in 2030 (ie, 11.2 million [10.1–12.4] chronic infections in 2030). Hepatitis C incidence will rise from 3.4 (95% UI 3.0–3.9) per 1000 person-years in 2018 (660 000 [580 000–750 000] incident HCV infections) to 4.1 (3.5–4.8) per 1000 person-years in 2030 (950 000 [820 000–1 100 000] incident HCV infections); the latter being an increase in incidence of 19.5% (12.5–27.1) relative to 2015 levels (figure 2; appendix p 40). If current levels of treatment are continued (SQ), 25.0% (95% UI 22.5–28.0) of chronic infections in 2018 would be cured by 2030, chronic hepatitis C prevalence and incidence would remain stable, but hepatitis C-related mortality would increase by 32.3% (25.0–40.0) relative to 2015 (figure 2; appendix p 40). Figure 2 shows the effect of each intervention scenario on hepatitis C mortality and incidence, with each cascade of care shown in figure 3.

For scenario S1, one-time screening of 90% of the general population in 2018–30 requires 13.8 million (95% UI 13.4–14.1) individuals or 6.2% (6.1–6.3) of the population being tested for hepatitis C antibody or RNA, or both, annually. On average, 350 000 (95% UI 315 000–385 000) treatments are started annually and 56.4% (54.8–58.0) of chronic infections in 2018 are cured by 2030 (appendix p 40). Compared with 2015 levels, incidence decreases by 26.5% (95% UI 22.5–30.7) by 2030 but mortality increases by 7.0% (1.1–13.5; figure 2). By 2030, both incidence and mortality are likely to decrease compared with baseline scenarios S0 and SQ.

Compared with scenario S1, scenario S2 (one-time screening with prioritisation for PWID and adults aged ≥ 30 years) results in the annual treatments increasing to 445 000 (95% UI 400 000–490 000) and 72.9% (71.4–74.3) of chronic infections in 2018 being cured by 2030 (appendix p 40). Incidence decreases by 40.8% (95% UI 36.4–45.4) and mortality by 14.8% (7.8–21.1) compared with scenario S0 for 2018–30 (figure 2).

For scenario S3, incorporating rescreening of previously treated individuals and individuals who previously tested antibody-negative increases the number of individuals screened by about 46.8%, compared with scenarios S1 and S2, to 20.2 million (95% UI 19.7–20.7) individuals annually. This increase results in 490 000 (95% UI 445 000–545 000) individuals being treated each year and 80.5% (78.2–82.8%) of chronic infections in 2018 being cured by 2030 (figure 3; appendix p 40). Incidence decreases by 50.8% (95% UI 46.1–55.0) and mortality by 17.9% (10.8–24.3%) compared with scenario S0 for 2018–30 (figure 2).

For scenario S4, incremental to scenario S3, doubling the primary screening rate (12.4% per year), improving treatment referral (90%), rescreening non-PWID every

5 years (instead of every 10 years), and re-engaging individuals who have been lost to follow-up back into care (every 5 years), substantially increased the number of people screened (via antibody or RNA testing) annually to 36.4 million (95% UI 35.1–37.8). Overall, 139.7% (95% UI 135.5–144.6) of the population in 2018 are screened by 2030 and 109.0% (107.0–111.4) of chronic infections in 2018 are cured, with 660 000 (595 000–735 000) being treated annually. Incidence decreases by 84.8% (95% UI 79.7–87.4) and mortality by 52.1% (43.0–59.3; figure 2), reaching a 65% reduction in mortality by 2035 (appendix pp 23, 40). The doubling in primary screening rate and the increase in referral had the most benefit in terms of reducing incidence (appendix p 24).

For scenarios S1–S4, the model suggests that one person will be treated for every 33–57 screening tests done, with scenario S2 achieving the lowest number of tests per treatment (appendix pp 25, 41).

For scenarios S1–S3, the median estimated cost of the different intervention scenarios for 2018–30 was \$3.4–5.1 billion (figure 4A), with the cost increasing for each successive scenario and 50–60% of costs being due to screening (appendix p 41). To reach the WHO elimination target for incidence (an 80% reduction), scenario S4 increases the total screening and treatment costs by two-thirds (*vs* scenario S3) to \$8.1 billion (95% UI 7.7–8.5) for 2018–30. The cost per cure is \$900–1200 for scenarios S1–S4 and is cheapest for scenario S2 (figure 4B).

Our sensitivity analyses showed that reducing the costs of either direct-acting antiviral regimens (X1) or diagnostic test kits (X2) to the lowest available price could each reduce total costs by 10% (*vs* the baseline of \$8.1 billion) to about \$7.2 billion separately, while including savings in health-care costs (X3) could reduce total costs by 13% to \$7.0 billion; figure 5). The inclusion of costs for improving referral and re-engaging patients who were lost to follow-up (X4) will probably have a minimal effect on total costs (<1% change). Notably, the implementation of a simplified screening and treatment pathway (X5) could have a considerable effect on costs, reducing the overall budget for eliminating hepatitis C by 16% to \$6.7 billion, while combining the effects of X1–X5 (X6) could reduce costs by 52% (*vs* the baseline) to \$3.9 billion by 2030. This saving results in a cost of \$600 per cure, with the annual costs equating to about 9.0% of the current health expenditure in Pakistan (2017–18 fiscal year)¹⁴—which is 0.11% of gross domestic product in 2017–18,²³ or about \$1.50 per person per year for the population in 2018. Changing the discount rate to either 0% (X7) or 7% (X8) varies the total costs by roughly 20%. Further reductions in costs of test kits and direct-acting antivirals, possibly due to bulk purchasing, would only decrease costs marginally, with a 25% reduction in both only decreasing overall costs to \$3.7 billion (appendix p 29).

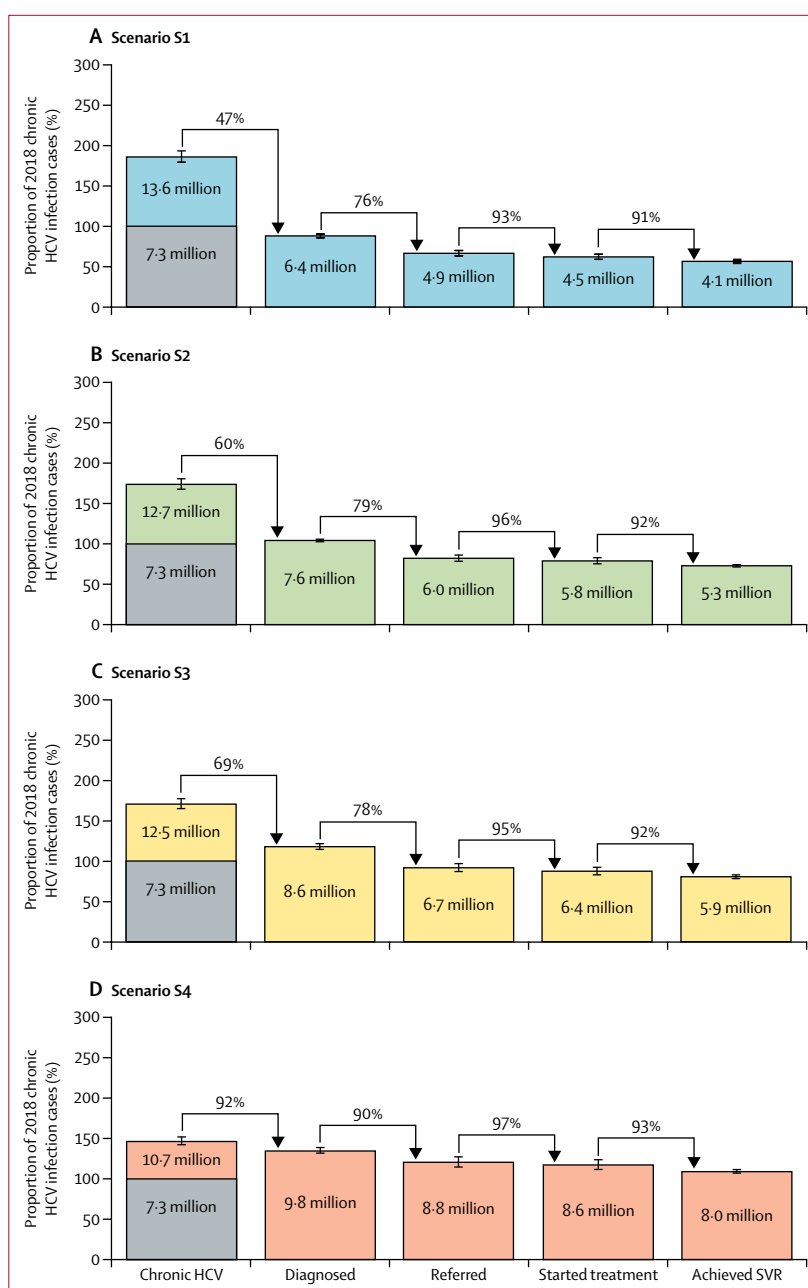


Figure 3: Cascade of care for scenarios S1–S4

Data are the median of 1151 final model runs. Error bars are 95% uncertainty intervals. The height of each bar is the proportion of cases (absolute numbers given within each bar) that are diagnosed, referred, initiated treatment, and achieved a sustained virological response relative to the chronic HCV burden in 2018 in the first bar corresponding to 100% (shaded in grey). The full height of the chronic HCV bar shows the full burden of HCV infections in 2018–30 for each scenario, which is the sum of the chronic HCV burden in 2018 with all new chronic infections that occur from 2018 until 2030 in that scenario. The arrows between each bar show the percentage of the previous step in the cascade of care that moves onto the following step. (A) Scenario S1: one-time random screening of 90% of the general population of Pakistan by 2030, with 80% referral to care. (B) Scenario S2: scenario S1 plus prioritised screening of people aged ≥ 30 years and PWID. (C) Scenario S3: scenario S2 plus rescreening of cured and previously antibody-negative or RNA-negative individuals from 2020 (every 10 years for non-PWID and annually for PWID). (D) Scenario S4: scenario S3 plus incremental improvements to achieve elimination. HCV=hepatitis C virus. PWID=people who inject drugs. SVR=sustained virological response.

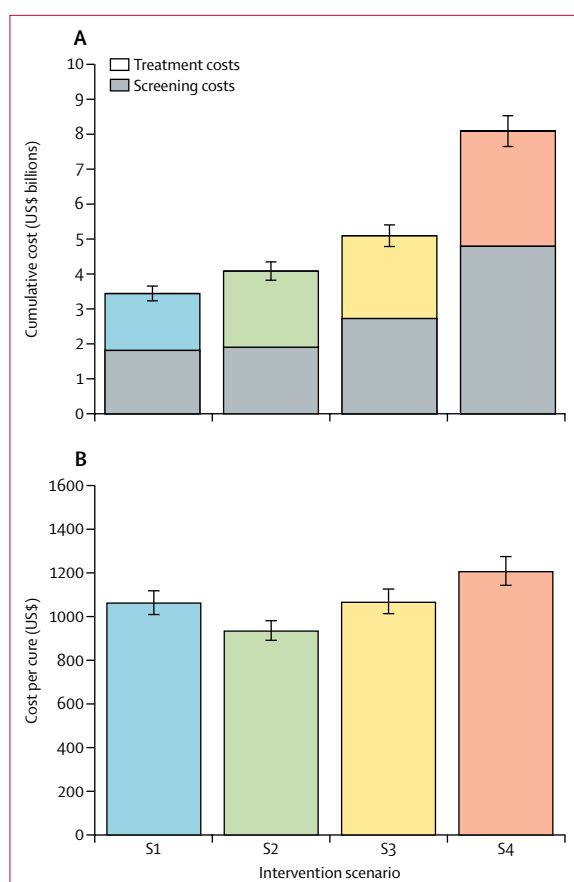


Figure 4: Estimated total screening and treatment costs (A) and median costs per cure (B) for each intervention scenario over 2018–30
Data are the median of 1151 final model runs. Error bars are 95% uncertainty intervals. Costs and outcomes are discounted at a standard rate of 3.5% per year. The proportion of total costs that are due to screening were 53% for S1, 47% for S2, 54% for S3, and 59% for S4. (A) Scenario S1: one-time random screening of 90% of the general population of Pakistan by 2030, with 80% referral to care. (B) Scenario S2: scenario S1 plus prioritised screening of people aged ≥ 30 years and PWID. (C) Scenario S3: scenario S2 plus rescreening of cured and previously antibody-negative or RNA-negative individuals from 2020 (every 10 years for non-PWID and annually for PWID). (D) Scenario S4: scenario S3 plus incremental improvements to achieve elimination. PWID=people who inject drugs.

Discussion

Our findings suggest that considerable screening of hepatitis C and effective referral to treatment is needed to achieve the WHO elimination target for hepatitis C incidence in Pakistan. Indeed, due to population growth and the expanding epidemic in Pakistan, our projections suggest that, to meet the target, 140% of the current Pakistan population (or 278 million people) will need to be screened for hepatitis C during 2018–30, 90% of diagnosed individuals will need to be linked to treatment, interventions will need to re-engage individuals who have been lost to follow-up, and regular rescreening will need to identify new reinfections. Although cheap treatments and diagnostics are available in Pakistan (the cheapest direct-acting antiviral is \$18 per 12-week treatment course), our estimates suggest that at its cheapest, this

screening and treatment strategy will cost US\$3.9 billion over 13 years, with the yearly costs making up 9.0% of the annual health budget of Pakistan (2017–18 fiscal year).¹⁴ This cost translates to about \$600 per cured individual.

Irrespective of the approach chosen, substantial improvements in the cascade of care for hepatitis C are required in Pakistan. First, primary antibody screening rates need to be high to identify prevalent and incident infections. The yield of this screening can be improved through prioritising high prevalence subgroups or using other risk-based criteria for deciding whom to screen.⁸ However, it is important that such risk-based screening algorithms are evaluated before being deployed to ensure that they capture most infections. Second, referral rates need to be high, as shown by Egypt's national testing and treatment programme, which has treated 88% of all diagnosed patients.²⁴ Development of improved diagnostics, such as point-of-care tests for active hepatitis C infection, could help with improving referral by simplifying the pathway from hepatitis C diagnosis to treatment,^{25,26} as achieved with HIV point-of-care testing in LMICs.²⁷ Simplifying the treatment pathway in other ways and using incentives or nurse facilitators to reduce loss to follow-up could also increase the number of individuals being referred to treatment.^{28,29} Lastly, because of continued risk of exposure to hepatitis C infection in the community, repeat screening is needed to identify reinfections; such rescreening is likely to incur substantial additional costs unless it can be targeted to those with identified risk.

Crucially, this work emphasises the immense effort and financial burden of a national hepatitis C elimination initiative in Pakistan. Our analyses show that a screen-all approach will be needed, requiring improved access to screening for all patient subgroups, including marginalised subpopulations—such as PWID, men who have sex with men, and patients with end-stage liver disease.³⁰

The main strength of our study is that, to our knowledge, it is the first to use detailed dynamic modelling to undertake a cost-impact analysis of what is needed to achieve the WHO hepatitis C elimination targets in a LMIC. In the Pakistan context, our cost estimates use local cost data based on real pathways of care to derive realistic cost projections for the actual implementation of screening and treatment in this setting. These budgetary estimates provide a basis to assess the economic feasibility of a large-scale hepatitis C screening and treatment programme for achieving hepatitis C elimination, which is crucial information for governments and other decision makers. The present modelling analyses have fed into discussions with the Government of Pakistan who, on World Hepatitis Day 2019, announced a new Prime Minister's Programme declaring the government's commitment to combating hepatitis C.³¹

Our analysis has several limitations. First, we did not include the added costs of improving the infrastructure

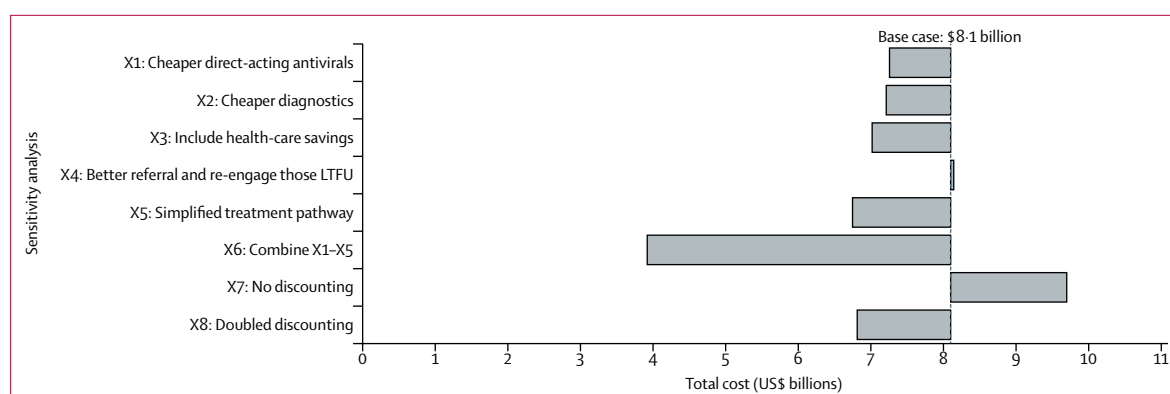


Figure 5: Univariate sensitivity analysis on total costs for scenario S4

We did sensitivity analyses to determine how the total costs of scenario S4 would vary for the eight changes in cost assumptions. X1: assume lowest Pakistan direct-acting antiviral drug costs (\$18 vs \$109 for 12 weeks); X2: assume lowest costs for diagnostic test kits (\$0.40 vs \$2.15 for antibody test, \$15 vs \$24 for RNA confirmation); X3: include savings in health-care costs for managing patients with hepatitis C-related disease; X4: include costs for improving referral from 80% to 90% of diagnosed chronic infections and reengaging people who have been lost to follow-up; X5: include savings from implementing a simplified treatment pathway (fewer visits and laboratory investigations); X6: combine X1 to X5; X7: no discounting of costs and outcomes (3.5% in base analyses); and X8: double the discount rate for costs and outcomes (3.5% in base analyses). Full details are in the appendix (pp 29, 34–35). LTFU=lost to follow-up.

in Pakistan to enable country-wide hepatitis C screening. Second, to estimate the cost savings related to prevented health-care provision for hepatitis C-associated morbidities, we adapted costs from Cambodia (appendix p 35) because data for Pakistan were not available. These savings offset 13% of the screening and treatment costs, emphasising the importance of obtaining local data to validate these estimates. Third, except for injecting drug use, we did not include any other risk-based stratifications in the model, so it was not possible to properly evaluate risk-based screening or rescreening, which could be more efficient than the screening scenarios we modelled. Moreover, although the model probably captures the main characteristics of how injecting drug use contributes to overall transmission of hepatitis C in Pakistan, added detail could be included on variations in the age that people start injecting drug use and their duration of injecting. Fourth, further modelling could also consider the effect and potential costs of scaling up prevention interventions, which preliminary projections (data not shown) suggest could dramatically reduce the screening and treatment required for achieving hepatitis C elimination, especially if the interventions are effective for the general population. However, evidence for the cost and effectiveness of suitable interventions for the general population do not exist, thus we did not include this scenario in our analyses. Fifth, we did not estimate the screening requirements and costs of achieving the WHO elimination target for mortality by 2030. In our analyses, even the most aggressive intervention (scenario S4) only reached the 65% mortality reduction target by 2035, possibly suggesting that the mortality target might not be feasible by 2030. Lastly, in Pakistan, health-care decisions are made at the provincial, rather than national, level following the devolution of

the national health programme in 2010.⁹ More detailed regional models are needed to determine geographical differences in the screening and treatment strategies needed in Pakistan's highly variable epidemics.

We have previously examined the required treatment scale up needed to reach the WHO elimination targets in Pakistan.⁵ This analysis builds upon our previous work by determining the screening requirements and likely costs of achieving these targets.

Few studies have examined the effects and budgetary implications of hepatitis C screening and treatment interventions in LMICs. A test-and-treat demonstration project studied the impact and cost-effectiveness of hepatitis C micro-elimination in rural Egypt.³² An analysis for South Africa considered the budgetary requirements for scaling up hepatitis C screening and treatment,³³ while analyses in eastern Europe and central Asia evaluated the cost-effectiveness of intervention packages for reducing hepatitis C transmission among PWID.³⁴ However, only the Egypt study³² used real context-specific cost data and none of these analyses incorporated the cascade of care into their models, nor did they estimate the level of screening and treatment needed for hepatitis C elimination. Moreover, the two analyses^{32,33} considering hepatitis C epidemics in the general population did not account for population growth or the effect of interventions on ongoing hepatitis C transmission, both of which are key factors characterising the hepatitis C epidemic in Pakistan and other LMICs.

One other study³⁵ considered the cost of achieving the hepatitis C elimination target for mortality in Pakistan. However, the projections were based on conservative assumptions for the number of incident hepatitis C infections (280 000 per year in 2018 instead of 660 000 in our model) occurring in Pakistan, likely due to the authors not modelling an increasing epidemic or

growing population; both of which are important characteristics of the Pakistan epidemic.^{5,36} Further, the health-care cost estimates in the previous study³⁵ were adapted from US data and staff costs were not included in the costs of treatment, meaning the cost estimates might not reflect the real costs in a Pakistan context. Our study improves on this analysis through using primary cost data from Pakistan and detailed epidemiological data to calibrate the increasing hepatitis C epidemic in Pakistan.

Pakistan is a crucial target country for achieving global hepatitis C elimination because it harbours 10% of the global hepatitis C burden. Our findings suggest that considerable scale up of screening and treatment interventions will be required at substantial cost to achieve the WHO hepatitis C elimination targets in Pakistan. Estimated annual screening and treatment costs could translate to around 9.0% of the current health expenditure of Pakistan (2017–18 fiscal year), with this equating to 0.11% of gross domestic product in 2017–18, or about \$1.50 per person per year.¹⁴ The government of Pakistan has already made substantial progress in starting hepatitis C prevention and control programmes⁹ and, although political will exists,^{9,36} greater health sector investment is required to effectively tackle the growing hepatitis C burden in Pakistan. Although specific to Pakistan, the insights from this study are applicable to other resource-limited settings with a high prevalence of hepatitis C. Our analyses show that the substantial costs of achieving hepatitis C elimination can be reduced dramatically through improving accessibility to cheaper drugs and diagnostics tests and by developing simplified screening and treatment algorithms. These findings could inform how other countries can work towards scaling up hepatitis C screening and treatment. To achieve global hepatitis C elimination, it is of paramount importance that hepatitis C epidemics be tackled in settings such as Pakistan that have a high burden of hepatitis C; widespread intervention scale up and resource investment should not be delayed.

Contributors

AGL and PV designed the study, interpreted findings, and wrote initial drafts of the manuscript. AGL developed the model and did all model analyses. GKG, HQ, HM, KA, GF, CF, HZ, AN, RA, QS, DM, SH, and AL provided epidemic data, treatment data, and cost data for the model. AGL, CFD, MTM, and AT analysed the epidemic data to parameterise the model. JGW collected and analysed the cost data, together with NM and AGL. AGL, JGW, NM, and PV interpreted findings from modelling the costs and budgetary impact. All authors contributed to the overall collaboration through guiding the analysis plan, interpreting the results, and critically reviewing the final version of the manuscript.

Declaration of interests

NKM has received unrestricted research grants and honoraria from Gilead and Merck unrelated to this work. PV has received unrestricted research grants and honoraria from Gilead, and honoraria from AbbVie. HF has received an honorarium from MSD unrelated to this work. MH has received unrestricted honoraria from Gilead, MSD, and AbbVie unrelated to this work. All other authors declare no competing interests.

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